Evaluation of New Anti-Infective Drugs for the Treatment of Vascular Access Device–Associated Bacteremia and Fungemia

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For clinical trials of anti-infective drugs for the treatment of vascular access device–related bloodstream infections, patients should be identified and enrolled on the basis of current standards for the clinical diagnosis of such infections. To ensure comparability of patients, only those infected with staphylococci and *Candida* species should be included. A prospective, randomized, double-blind design is recommended. Future protocols may include abbreviated courses of therapy, treatment with combinations of drugs, or a progression from parenteral to oral therapy. Clinical response is judged as cure, failure, or indeterminate response; there is no "improved" category. Microbiological response is categorized as eradication, persistence, or relapse and is of paramount importance. Several months of follow-up may be necessary for the detection of late relapses or metastatic infections. This guideline does *not* apply to studies of bacteremia or fungemia secondary to non-device-related, organ-based primary infections (e.g., pneumonia, urinary tract infection), which should be assessed in relation to the primary disorder.

I. INTRODUCTION

This guideline is one of a series of disease-specific guidelines that have been prepared to assist sponsors and investigators in the development, conduct, and analysis of studies of new anti-infective drugs. This guideline deals with the conduct of phase 1 through phase 4 clinical trials and is a subset of the General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products and of the European Guidelines for the Clinical Evaluation of Anti-Infective Drug Products [1], which should be consulted for the prerequisites to the conduct of studies in humans. Lack of coverage in this specific guideline of issues covered by the General Guidelines does not imply that these issues are unimportant.

A. Standards of Care

The standards of care for vascular access device–associated bloodstream infections are based on the patient's history, the natural history of the disease, and currently available therapy [2–4]. These infections pose an expanding problem. Invasive therapeutic and monitoring devices, which are being used with increasing frequency and which compromise the vascular integrity of hospitalized patients and of other individuals as well (e.g., those undergoing parenteral therapy at home), provide a route by which pathogens can gain access to the bloodstream and cause metastatic infection. Factors such as the type and nature of the device, its anatomic site, the duration of its use, the quality of local care at cutaneous access sites, and other medical practices may influence the frequency and nature of these infections. The clinical presentation of fever, phlebitis proximal to the cutaneous entry site, and hypotension suggests this diagnosis.

1. Bacteremia

Device-associated bacteremia frequently involves *Staphylococcus aureus* and coagulase-negative staphylococci. Gram-negative bacilli and *Streptococcus pyogenes* are less frequently involved.

2. Fungemia

Candida species are the fungi most frequently responsible for device-related infection. As there is no well-defined or established standard of therapy for device-associated fungemia, use of historical control groups cannot be recommended. In vitro susceptibility to antifungal agents varies among species, and this variability must be considered in the selection of treatment.

3. Confounding Factors

Devices impregnated with anti-infective substances are now employed in many health-care settings. Their use may

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influence the nature of the infecting organisms and may confound analyses of the safety and efficacy of study drugs [5].

B. Scope of the Guideline

1. Clinical Entities Included

This guideline applies to protocols for evaluation of the safety and efficacy of new anti-infective drugs in the treatment of device-associated bloodstream infections due to *Staphylococcus* and *Candida* species. Peripheral or central intravenous devices, venous or arterial pressure monitoring devices, pacemakers, and balloon-assist devices are all potential sources of such infections.

2. Clinical Entities Not Included

This guideline does not cover device-associated bloodstream infections due to organisms other than *Staphylococcus* or *Candida* species, local device-associated infections without evidence of bloodstream involvement, or secondary bloodstream infections related to underlying organ-based pathology (e.g., pneumonia).

C. Future Trends

At present, the diagnosis of device-related bloodstream infections is founded on the growth of a bacterial or fungal species from cultures of a removed device and the demonstration of the same organism in cultures of venous blood drawn when the device was in place. The use of surrogate markers, such as microbial antigens in body fluids, for the diagnosis of device-related bloodstream infections in clinical trials is not currently recommended.

Interpretation of a positive culture of a removed device is not always straightforward. Semiquantitative cultures should be performed and interpreted by established criteria [6].

II. DEFINITIONS OF THE DISEASE

Both clinical and blood-culture criteria can be useful for the definition of device-associated bloodstream infection.

A. Device-Associated Bacteremia

Definite device-associated bacteremia is defined by one or more cultures of removed device surfaces that are positive for a given organism in addition to two cultures of venous blood that are obtained from a site remote from the device and are positive for the same organism [6]. The isolation of *different* organisms from device surfaces and blood should be designated "unable to evaluate." Culture of catheter hubs is not an acceptable diagnostic technique for clinical trials. *Probable* device-associated bacteremia is defined by positive cultures of the same organism from two separate venous-blood samples obtained from a site remote from the device with an intervening interval of $\geq$15 minutes. *Possible* device-associated bacteremia is defined by two positive cultures of the same organism from blood aspirated from the device or by two positive cultures of the same organism from purulent material collected from the cutaneous entry site.

B. Device-Associated Fungemia

The criteria for the definition of device-associated fungemia are the same as those for device-associated bacteremia. The isolation of *Candida* species from a single blood culture may be sufficient for a given study, but the use of this criterion must be clearly justified in the protocol.

III. INFORMATION NEEDED BEFORE CONDUCTING CLINICAL TRIALS

A. In Vitro Studies

An antimicrobial drug subjected to clinical trials of therapy for bacteremia or fungemia must exhibit in vitro activity against the pathogens whose isolation is anticipated. The number of strains tested for susceptibility should be sufficient for the accurate determination of the MIC_{90}. Automated or tube dilution methods may be employed with standard microbiological techniques. The method for determining the MIC should be stated clearly in the protocol. The size of the inoculum should conform to that used in standardized methods and should be explicitly described in the protocol. Determinations of the MBC, the serum bactericidal titer, time-kill curves, or other indicators of in vitro antimicrobial activity are desirable but not required. Because the results of such tests are highly dependent on the method being used, methods must be described in detail. The inoculum size should be adequate to determine >99.9% killing and to minimize or eliminate antimicrobial carry-over. The techniques used for obtaining samples and processing blood cultures should be specified clearly. The source of cultured blood (i.e., blood collected by phlebotomy vs. blood aspirated from the implicated device) must be stated. The in vitro susceptibility of fungi to drugs is poorly predictive of in vivo efficacy. Therefore, other justification must be provided to regulatory authorities for the selection of particular drugs and regimens to be studied.

B. In Vivo Studies

It is desirable (especially with regard to antifungal chemotherapy) to conduct tests with animal models of experimental infection before trials are initiated in humans. To date, the extrapolation of results from animal models to humans has resulted in more accurate prediction of the failure of a

specific antimicrobial regimen than of its success. Clinical trials in humans may not be justified if a drug has been shown to be ineffective in experimental bloodstream infection at dosages thought to be applicable to humans. For both bacteremia and fungemia, studies of animal models of endocarditis may be appropriate before trials involving patients are initiated. [8–10].

IV. QUALIFICATIONS OF INVESTIGATORS AND INSTITUTIONS

A. Investigators

See General Guidelines [1], section VII.

B. Institutions

The institution conducting a clinical trial should have a clinical microbiology laboratory that can perform the following tests: (1) determination of the MIC; (2) determination of the concentration of an antimicrobial drug in serum; and (3) identification (to the species level) of microorganisms recovered from cultures of blood, access sites, and/or removed devices. Alternatively, participating centers may refer samples for processing at a single laboratory that is certified by recognized authorities and employs personnel skilled in the procedures to be used.

V. DESIGN AND IMPLEMENTATION OF PHASE 1, 2, AND 3 CLINICAL TRIALS

See General Guidelines [1], sections III and VI.

VI. ELEMENTS TO BE CONSIDERED IN DESIGNING PHASE 2 AND 3 CLINICAL TRIALS

A. General Considerations and Demographic Characteristics

The number of evaluable patients in each arm of a study should be sufficient to detect clinically important differences, as defined in the protocol. There are no underlying illnesses that absolutely preclude participation. No age limitations for participants are standard, although phase 1 studies may indicate that such limitations are needed. Studies of children should be conducted separately from those of adults whenever feasible.

While two well-controlled studies are recommended, a single, well-designed, randomized, controlled, and preferably double-blind study of adequate size may, under certain circumstances, be considered an adequate basis for registration of a new anti-infective agent.

B. Inclusion Criteria

Patients enrolled in clinical trials should have a clinical picture including signs and symptoms of acute infection (e.g., fever, rigors, inflammatory phlebitis in the device access area) plus isolation of an appropriate pathogen from cultures of (1) blood (obtained via the device or by peripheral phlebotomy), (2) a roll-plate sample from the removed device surface, and/or (3) the device access site.

C. Exclusion Criteria

See General Guidelines [1], section IX.B. In addition, patients with the following conditions should not be enrolled: (1) more than 24 hours of prior therapy with an antimicrobial agent active in vitro against the isolated pathogen; (2) hypersensitivity to the study drugs; (3) pregnancy; (4) severe renal dysfunction or hepatic dysfunction unless otherwise specified in the protocol; or (5) evidence of acute urinary tract, pulmonary, or abdominal infection or of another (nondevice) potential source of bloodstream infection.

If antimicrobial agent–impregnated device/catheter substances are used in a study, the protocol must include specific justification for their use.

D. Special Conditions

(1) Specific details of device management (e.g., device-site care, device removal before or during therapy, device replacement) must be recorded along with temporal references to therapy and diagnosis.

(2) Inflammatory phlebitis should be quantified when present. Photographic documentation is desirable but not required.

(3) Consideration should be given to stratification for trial design, such as (a) type of catheter (peripheral vs. central/long-dwell); (b) management of the device (i.e., removal of the implicated device before or during therapy, leaving the device in place throughout the study, or placement of a new device over a guidewire at the initial infection site); (c) inclusion or exclusion of neutropenic hosts; and (d) type of material making up the device.

(4) Local device-site care procedures, as addressed in the protocol, should be standardized as much as possible [7, 11, 12].

E. Selection of the Comparison Drug(s)

The drugs chosen for comparison with the study drug(s) in studies of bacteremia must be active against the presumptive staphylococcal pathogens (e.g., vancomycin). The agents selected for comparisons in studies of fungemia must be active against *Candida* species (e.g., amphotericin B); azole antifungal drugs may be acceptable comparison agents in some

settings, but their use for the treatment of immunocompetent patients is still being investigated.

Noncomparative trials of device-related bacteremia or fungemia require justification.

F. Study Design

All studies should be (1) double-blind, unless this type of design is precluded by the choice of the comparison formulation (e.g., amphotericin B) or by other conditions; (2) randomized; (3) stratified (with a maximum of three strata pre hoc); and (4) structured to include statistical-power assumptions that allow for the detection of clinically relevant differences (see General Guidelines, section XV and Appendix). Whenever possible, studies should be prospective. Studies should be designed to ensure that no more than 25% of cases are within the "possible" category (see section II of this guideline) or involve atypical devices, such as pacemakers. All protocols should be designed to include information on device dwell time before infection and on access-site care. See General Guidelines [1], section XI, for further discussion of issues arising in the design and stratification of studies.

G. Administration of the Study Drug

Initial treatment with the study drug in phase 2 or phase 3 trials should be based on preclinical investigations that demonstrate efficacy in vitro and (when possible) in animal models. Choices regarding dosage, schedule, and other pharmacokinetic considerations should be based on the results of previously completed phase 1 trials supporting the safety and efficacy of the drug in question. Antimicrobial susceptibility should be assessed in vitro as soon as an etiologic organism is isolated. Should the strain be resistant to the test drug, the study should be terminated and the patient given an antimicrobial drug known to be effective against the causative microorganism, unless prior approval from regulatory authorities has been obtained.

In the initial studies, the duration of therapy with the test drug should be the same as that of treatment with standard agents. If outpatient therapy is considered desirable or feasible, patients must be examined regularly for evidence of clinical or microbiological failure of treatment and for toxic or adverse effects. In addition, compliance with outpatient therapy must be ensured.

Depending on the pharmacological and antimicrobial characteristics of the study drug, it may be possible to switch from parenteral to oral therapy. The protocol should state clearly the point at which such a conversion may take place and the measures that are planned to ensure adequate absorption of an orally administered drug. The duration of therapy should be clearly defined in the protocol (usually, a minimum of 7–10 days) [2, 11, 13].

H. Definition of Response to Therapy

1. Clinical Response

The primary measures of efficacy should be clearly described in the protocol. Clinical responses can be classified as cure (resolution of all signs or symptoms noted at enrollment); failure (persistence of presenting signs or symptoms, development after enrollment of any new unfavorable findings relating to efficacy measures, and/or removal of the implicated device after initiation of therapy); or indeterminate (antimicrobial therapy during the period of follow-up that precludes clinical evaluation). Therapy resulting in an indeterminate response must be justified in the case report form. If such justification is lacking, the case should be categorized as a failure.

2. Microbiological Response

Cultures of samples obtained during therapy (usually within 72 hours of its initiation) and at least 7 days after the completion of treatment are a requisite for the evaluation of bacteriologic response. The categories of response are eradication or cure (posttreatment culture demonstrating an absence of the initial pathogen); persistence or failure (posttreatment culture yielding the initial pathogen); superinfection (follow-up culture demonstrating eradication of the initial pathogen but emergence of a new pathogen); and relapse. Other possible categories of bacteriologic response are defined in the General Guidelines [1], section XIII.C.

3. Final Assessment/Duration of Follow-Up

The test of cure is undertaken at the early follow-up visit, which should take place ~7 days (range, 5–9 days) after the completion of therapy, unless stated otherwise in the protocol. A late follow-up assessment 28–35 days after the completion of therapy is highly desirable.

I. Methods of Assessing Safety

See General Guidelines [1], section XIV. In addition to the elicitation of a complete history and the performance of a physical examination, a complete blood count, a chemistry profile, and urinalysis should be undertaken 1 week after treatment in all cases and at other times during follow-up if clinically indicated. The suggested laboratory tests represent the minimal requirements for the evaluation of patients with bloodstream infections. Additional testing related to preclinical or pharmacological data on the toxicology of the study drug is warranted to ensure accurate monitoring of safety.

Table 1. Summary of the guideline for evaluation of new anti-infective drugs for the treatment of intravenous device–associated bacteremia and fungemia.

Type of assessment	Requirement at indicated point		
	Before therapy	During therapy	After therapy
Clinical	Complete history/physical examination	Daily assessment	Assessment immediately after therapy, at 5–7 d, and at 1 mo
Laboratory	Routine panel* (hematology, chemistry)	Selected indices (protocol-specific)	Routine panel
Microbiological	Baseline cultures: blood (requisite), device, access site	Blood culture (at 3–5 d)	Blood culture immediately after therapy, at 7 d, and at 1 mo
Monitoring	. . .	Serum drug concentrations, routine parameters (vital signs), device site (descriptors)	. . .

* Panel applicable to specific studies in the protocol.

J. Methods of Presenting and Analyzing Data

See General Guidelines [1], section XVI and Appendix. Specific subgroup analyses (i.e., removal vs. continued presence of device during therapy) can be anticipated, and subgroups should be defined before initiation of the study.

K. Methods of Assuring Compliance or Ethical Conduct

See General Guidelines [1], sections IV and XI.E.

VII. INFORMED CONSENT

See General Guidelines [1], section IV.D. Informed consent must be obtained from participants or their guardians before enrollment in the study, according to the regulations of the local institutional review board.

VIII. SUMMARY OF THE GUIDELINE

The main points of this guideline are summarized in table 1.

The European Working Party

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